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## More Vaccines on the Horizon

By Joshua Lederberg

VACCINATION was introduced into medical practice by Jenner's use of cowpox as a preventive against smallpox. It has since become one of the major triumphs of medicine. Founded on this blind empiricism, the procedure has been extended to a great many other diseases by the application of a new science of virology. In fact, vaccination is the only important way we now have to cope with virus infections, such as smallpox, polio, rabies, yellow fever, influenza and measles.

### Science and Man

We see on the horizon vaccines for rubella (German measles), mumps and chickenpox. The possibility that some tumors may be caused by viruses is still a conjecture based on animal experimentation, but if it can be substantiated it will point to the chance to develop vaccines against the corresponding viruses.

The vaccine usually works by provoking the inoculated host to make antibodies. These are modified globulin proteins capable of recognizing and neutralizing virus particles while they are in the bloodstream and other body fluids in transit from an infected cell to a fresh one. The antibody reaction is extremely specific. Hence the vaccine must contain particles closely similar to those causing the disease.

Modified viruses of two kinds are used: chemically altered particles ("killed viruses") unable to propagate in the host, and genetic mutant virus strains ("attenuated viruses") which are still capable of limited propagation, but whose biological properties are altered to prevent serious

disease after their artificial introduction into the host organism.

Killed vaccines must usually be injected to enable them to reach the antibody-forming tissues. Attenuated viruses can often be taken by mouth and, in view of their own propagation, in much smaller doses. Furthermore, their persistence in the body usually leads to a much longer immunity, sometimes for an indefinite period.

Attenuated viruses are therefore cheaper than killed viruses—both to administer, because no injection is needed, and to prepare, because there is less virus per dose and less attention must be paid to chemical modification.

The Salk polio vaccine is the best known example of a killed vaccine. Virulent poliovirus is killed with formaldehyde. Sabin polio vaccine is a live attenuated vaccine which uses carefully selected strains of poliovirus.

THE DEVELOPMENT of a vaccine then goes through three principal phases 1) the close study of a disease and the successful isolation of a causative virus 2) the development of practical techniques to produce the virus on a large scale and an assay of it and 3) the discovery of reliable modifications, either chemical inactivation or an attenuated mutant strain. The third phase still raises many scientific questions in spite of its empirical success so far.

Salk's procedure of formaldehyde-inactivation demanded the most meticulous attention for reliable results.

Attenuated mutants are equally empirical, with the possibility always remaining that virulence might return under odd conditions—like unexpected routes of attack, or weakening of the host by

disease, or malnutrition or concurrent drug therapy.

Any complacency we might have had about the foundations of virology was badly shaken by our experience with polio vaccination in the last decade. Overall, this was a triumph.

As was learned only five years later, starting in 1955 many millions of children who were inoculated with polio vaccines also received a contaminating virus, SV-40, derived from the monkey tissues on which the virus was grown. This virus has not subsequently been proven to exert any harmful effect. It was the purest good fortune that this was not the worst medical catastrophe in history. SV-40 virus is known to be able to cause tumors when injected into newborn hamsters, and can be detected by effects on tissue cultures of cells from many species, including man.

Virology is still too primitive to give absolute assurance against the repetition of such incidents, or others we still are too ignorant to ask about. We can ill afford not to make utmost practical use

of empirical vaccines. However, we will be severely punished in the long run if we do not sharpen our vision—down to the molecular level—in our use of these agents.

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